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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,461	12/04/2003	John D. Shaughnessy	D6485	6235

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/727,461	**Applicant(s)** SHAUGHNESSY, JOHN D.
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 April 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *15,18 and 19*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Response to the Amendment

The Amendment filed on 4/12/2006 in response to the previous Final Office Action (1/12/2006) is acknowledged, but has not been entered because the entrance of the amendment would necessitate a new search and consideration with respect to patentability under 112, first paragraph.

Claims 15 and 18-19 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 15 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a method of determining the risk of developing bone disease in a test individual comprising examining the expression level of a WNT signaling antagonist, wherein increased expression of the antagonist compared to that in a normal individual indicates that said test individual has the risk of developing bone disease. Claims must be interpreted as broadly as their terms reasonably allow. Thus, the claims read on a method of determining the risk of a bone disease, which encompasses bone diseases that have yet to form in the mammal.

However, the instant claims are not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to determining the risk of developing any and/or all bone disease in a test individual comprising examining the expression level of a WNT signaling antagonist, wherein increased expression of the antagonist compared to that in a normal individual indicates that said test individual has the risk of developing bone disease. The specification teaches that 174 patients with "newly" diagnosed multiple myeloma, 16 patients with monoclonal gammopathy of undetermined significance, 9 with Waldenstroms macroglobulinemia, and 45 normal persons were studied in the present invention (page 27, lines 10-16). The specification further provides (page 35, Example 8) an analysis of the results obtained from 173 patients with myeloma, wherein the DKK1 signal for patients with 1 + MRI and no x-ray lesion differ significantly compared to patients with no MRI and no x-ray lesions, but does not differ significantly compared to patients with 1 + MRI and 1 + x-ray. Moreover, the specification teaches (page 9, Example 9) a correlation between global gene expression of DKK-1 and lytic bone lesions in multiple myeloma. Thus, while the specification clearly teaches a diagnosis of bone disease in a multiple myeloma patient comprising comparing the level of DKK-1 expression in an individual with multiple myeloma compared to a "normal" individual, the specification appears to be silent on how to interpret this as a method of determining the risk of developing any and/or all bone disease.

In the instant case, the closest prior art, McCarthy (WO 0052047, 2000), to the claimed invention teaches human dickkopf-related proteins (referred to herein as DKK) and uses thereof, wherein one activity associated with the DKK family of proteins is the modulation, e.g., antagonism, of the activity of the Wnt family of secreted proteins (page 23, lines 16-18). Specifically, the WO document teaches a method of diagnosing a disease or disorder associated with aberrant expression

or activity of DKK (abstract). While McCarthy contemplates determining the risk of developing a disease associated with aberrant expression or activity of a DKK protein (page 96, lines 14-16), there does not appear to be any demonstration that the DKK family of proteins can be used to determine risk.

Those of skill in the art recognize that reasonable guidance with respect to assessing the risk of any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and monitored over some period of time prior to the disposition of cancer. The majority of the initial data may be derived from widespread genetic analysis, cancer clusters, or family histories. For example, Chappuis et al. (Cancer Treat Res. 2002; 107: 29-59) discloses an analysis of risk assessment and the importance of genetic testing in ovarian cancer. Specifically, Chappuis et al. teaches that in ovarian cancer, family history is one of the strongest known risk factors, wherein approximately 5 to 13% of all ovarian cancer cases are caused by the inheritance of cancer predisposing genes with an autosomal pattern of transmission (abstract). In addition to genetic factors, McLaughlin et al. (Tannock, I.F. and Hill, R.P., The Basic Science of Oncology, Chapter 2, (3rd Ed., 1998)) teaches that there are a plethora of environmental factors ar which are also determinants for cancer risk in a population. Some environmental factors disclosed by McLaughlin et al. include exposure to tobacco products, dietary factors, alcohol and occupational exposure (page 16). In the instant case, the specification is devoid of any models or experimental analysis that reasonably suggests that the claimed method would predictably determine the risk of the development of a bone disease in an individual. This, combined with the state of the art of preventing cancer, suggests that undue experimentation would be required to practice the invention as broadly claimed.

In response to the rejection, Applicants contend that the claim 15 has been amended to recite a method of diagnosing a Wnt antagonist-associated lytic bone disease in an individual comprising examining the expression of the human homologue of Sickkopf-1 (DKK-1) protein in an individual, where an increased expression of the protein compared to that in a normal individual indicates that the individual has the risk of developing the Wnt antagonist-associated lytic bone disease. As such, Applicants assert that the Wnt signaling pathway is critical for osteoblast differentiation and function. Interesting, Applicants submit that the expression level of two Wnt-signaling antagonist, Dkk-1 and FRZB, were not only expressed in a greater number of lytic bone

lesions from patients diagnosed with multiple myeloma compared to the multiple myeloma patients lacking bone lesions, but were expressed at higher levels in plasma cells of focal lesions than in bone marrow aspirates. Moreover, Applicants submit that the instant specification also discloses a positive correlation between DKK1 gene expression and level of DKK1 in bone marrow plasma in patients diagnosed with myeloma using ELISA. Applicants further argue that the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue amount of experimentation (MPEP 2164.02). As such, Applicants assert that the diseases such as multiple myeloma, osteoporosis, post-menopausal osteoporosis, malignancy-related (prostate cancer metastasis, breast cancer metastasis) bone loss are known in the art to be associated with bone lysis. Therefore, given the teachings in the instant specification, one skilled in the art can easily diagnose an individual suffering from any one of these diseases with Wnt antagonist-associated lytic bone disease by comparing the expression level of DKK-1 protein of such individuals with the expression of the protein of normal individuals.

As Applicant's arguments appear to be solely drawn to the currently filed amendment which has not been entered, such arguments have not been considered.

Therefore, because the specification only appears to suggest diagnosis of bone disease in a multiple myeloma patient by comparing the level of DKK-1 expression in an individual with multiple myeloma compared to a "normal" individual and is silent on how to interpret this as a method of determining the risk of developing any and/or all bone disease, undue experimentation would be required to practice the invention as broadly claimed.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER